EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3888	aggarwal	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:42
L2	453	L1 and (septic or sepsis)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L3	2	"6465511".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:44
L4	2	"7022734".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L5	2	"5593964".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L6	2	"6552071".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L7	2	"7235644".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L8	2	"20050288218".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L9	2	"20040214795".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L10	2	"6132610".pn.	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L11	11	"1226821"	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:43
L12	4634	nfkb or (transcription adj factor adj nf)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:45
L13	2632	l12 and ((septic ajd shock) or sepsis)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:46
L14	4844	nfkb or (transcription adj factor adj nf) or (nuclear adj factor adj kb)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:45
L15	2726	l14 and ((septic ajd shock) or sepsis)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:46

EAST Search History

L16	2683	l15 and (induce? or activat? or inducing)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:46
L17	1465	l16 and (liposaccharide or lps)	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:46
L18	475	l17 and ((liposaccharide or lps) adj (activated or induced or activat? or induc?))	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:56
L19	2	"9961030"	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:56
L20	1	"99061030"	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:56
L21	0	"1999061030"	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:56
L22	2	"9961030"	US-PGPUB; USPAT; DERWENT	OR	ON	2007/07/18 13:56

The Practical Peer-Reviewed Journal for Primary Care Physicians

Postgraduate Medicine online

symposium

Optimal management of septic shock

Rapid recognition and institution of therapy are crucial

Stephen J. Fitch, MD; James R. Gossage, MD

VOL 111 / NO 3 / MARCH 2002 / POSTGRADUATE MEDICINE

CME learning objectives

- To understand the importance of organ hypoperfusion in **septic shock**
- To become familiar with various vasoactive agents used in **septic shock**
- To review the role of fluids in treatment of **septic**

shock

*The authors disclose **no** financial interest in this article.*

This is the second of two articles on critical care.

This page is best viewed with a browser that supports tables.

Preview: **Septic shock** is the most common cause of death in intensive care units in the United States, and its incidence is rising. This growth is most likely due to the increased use of invasive devices and immunosuppressive therapies, higher numbers of immunocompromised patients, and increasing antibiotic resistance. In this article, Drs Fitch and Gossage discuss the natural history and diagnosis of **septic shock** and optimal management, including optimization of organ perfusion, fluid therapy, and use of vasoactive agents.
*Optimal management of **septic shock**: rapid recognition and institution of therapy are crucial. Fitch SJ, Gossage JR. Postgrad Med 2002;111(3):53-66*

About 400,000 cases of sepsis, 200,000 cases of **septic shock**, and 100,000 deaths from both occur each year in the United States (1). Sepsis is defined as the systemic response to infection (2). In the absence of infection, it is called systemic inflammatory response syndrome and is characterized by at least two of the follow-ing: temperature greater than 38°C or less than 36°C; heart rate greater than 90 beats per minute; respiratory rate more than 20/minute or $Paco_2$ less than 32 mm Hg; and an alteration in white blood cell count (>12,000/mm^3 or <4,000/mm^3).

Septic shock is a subset of severe sepsis defined as sepsis-induced hypotension that persists despite fluid resuscitation and is associated with tissue hypoperfusion. Patients receiving vasoactive agents are also considered to have **septic shock** if they have tissue hypoperfusion despite correction of the hypotension.

Natural history

The last 30 years have yielded much information about the underlying abnormalities in **septic shock**, but many unanswered questions remain regarding the pathophysiology of this process. A detailed discussion of the molecular events associated with **septic shock** is beyond the scope of this article. However, it is important to understand the underlying cytokine cascade (figure 1). Local inflammation and substances elaborated from organisms, especially endotoxin, activate neutrophils, monocytes, and tissue

SHOCK®

Injury, Inflammation, and Sepsis: Laboratory and Clinical Approache

Induction of Early Inflammatory Gene Expression in a Murine Model of Nonresuscitated, Fixed-Volume Hemorrhage.

Basic Science Studies

Shock. 17(4):322-328, April 2002.

*Rajnik, Michael *; Salkowski, Cindy A. +; Thomas, Karen E. +; Li, Ying-Yue ++; Rollwagen, Florence M. ++; Vogel, Stefanie N. +*

Abstract:

The etiology of many end-organ problems associated with hemorrhage has been attributed to the inflammatory response to hemorrhage. In a murine model of nonresuscitated, fixed-volume hemorrhage, we sought to elucidate the role that hemorrhagic insult alone plays in the generation of the early inflammatory cascade. Differences could be appreciated as early as 1 h post-hemorrhage, with consistent differences detected by 3 h in all of the major cytokine genes studied. Significant upregulation of IL-1[beta], IL-6, TNF-[alpha], and IL-10 mRNA expression was observed in both the liver and lung samples of mice subjected to fixed-volume hemorrhage when compared with sham-hemorrhaged mice. The cyclooxygenase-2 (COX-2) and inducible nitric oxide synthetase (iNOS) genes also were upregulated in the livers and lungs of hemorrhaged mice. Finally, expression of the genes that encode the Toll-like receptors (TLR)-2 and -4 was increased by hemorrhage. Taken collectively, these data demonstrate that the initial inflammatory cascade associated with hemorrhage occurs within hours after the initial hemorrhagic event, and can be associated with significant modulation of expression of key pro- and anti-inflammatory cytokine, enzyme, and TLR genes, suggesting that these may be possible new therapeutic targets.

macrophages. This results in a cascade of proinflammatory and anti-inflammatory cytokines and other mediators, such as IL-1, IL-8, IL-10, tumor necrosis factor-alpha, prostaglandin E_1, endogenous corticosteroids, and catecholamines. Effects of this complex mediator cascade include cellular chemotaxis, endothelial injury, and activation of the coagulation cascade. An imbalance in favor of anti-inflammatory cytokines may result in relative immunosuppression and, if persistent, in increased risk of death (3).

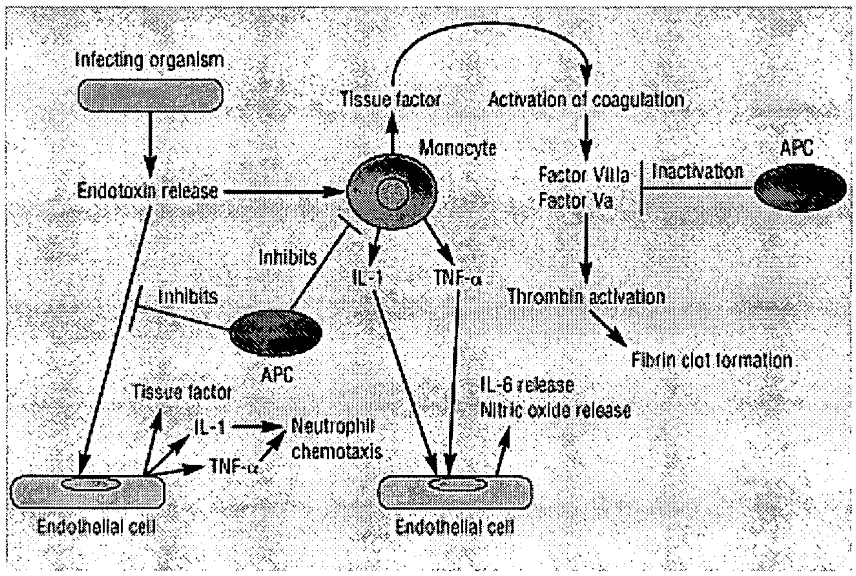

Figure 1. Events associated with major mediators of cytokine cascade in septic shock. Endotoxin and other antigenic components of infecting organism stimulate monocytes and local endothelial cells, resulting in elaboration of IL-1, tumor necrosis factor-α (TNF-α), and tissue factor (primary stimulant for coagulation cascade). Activated protein C (APC) is shown to inhibit several areas of pathway.

The initial cardiovascular response includes decreased systemic vascular resistance and depressed ventricular function. Low systemic vascular resistance occurs in response to substances elaborated from infectious agents, cytokines, mediators such as nitric oxide, and down-regulation of peripheral catecholamine receptors. The origin of the decreased ventricular function is unknown, but various inflammatory mediators and tissue edema have been implicated (4).

If this initial cardiovascular response is uncompensated, generalized tissue hypoperfusion results. Aggressive fluid resuscitation may improve cardiac output and systemic blood pressure, resulting in the typical hemodynamic pattern of **septic shock** (ie, high cardiac index and low systemic vascular resistance). The response to volume loading in survivors of sepsis is ventricular dilatation (4,5); nonsurvivors may show little change in cardiac output. However, despite improvement in central hemodynamics, abnormalities in regional and microcirculatory blood flow often persist. These abnormalities may lead to cellular dysfunction, lactic acidosis and, ultimately, multiorgan failure. Death from **septic shock** usually results from rapid and overwhelming progression of sepsis unresponsive to all

therapeutic maneuvers, multi-organ failure, or secondary nosocomial infection or complication.

Diagnosis

A patient who is hypotensive and in **shock** should be examined and treated as soon as possible. The evaluation should focus on differentiation of **septic** or hyperdynamic **shock** from other types, identification of the site of infection, and monitoring for end-organ dysfunction. Pertinent history should be obtained and a physical examination performed.

The early phases of **septic shock** may produce evidence of volume depletion, such as dry mucous membranes, and cool, clammy skin. After resuscitation with fluids, however, the clinical picture is typically more consistent with hyperdynamic **shock**, including tachycardia, bounding pulses with a widened pulse pressure, a hyperdynamic precordium on palpation, and warm extremities. Signs of possible infection include fever, localized erythema or tenderness, consolidation on chest examination, abdominal tenderness, and meningismus. Signs of end-organ hypoperfusion include tachypnea, oliguria, cyanosis, mottling of the skin, digital ischemia, abdominal tenderness, and altered mental status. Often, a definitive diagnosis cannot be made on the basis of initial findings on history taking and physical examination, and treatment for several possible conditions commences simultaneously.

Laboratory studies should include measurement of arterial blood gases, lactic acid level, electrolytes, renal function, and liver enzyme levels, as well as a chest radiograph. Cultures of blood, urine, and sputum should be obtained before antibiotics are administered. Cultures of pleural, peritoneal, and cerebrospinal fluid may be appropriate in some patients. If thrombocytopenia or bleeding is present, tests for disseminated intravascular coagulation should be performed (fibrinogen, d-dimer assay, platelet count, peripheral smear for schistocytes, prothrombin time, and partial thromboplastin time). It is important to compare the potential benefit of each diagnostic test or procedure with the time lost at the bedside attending to the fundamental goals of ensuring good gas exchange and tissue perfusion.

Treatment

Meticulous supportive care increases the likelihood of survival. The importance of adopting an aggressive tempo of resuscitation cannot be overemphasized. Almost all the interventions in early management of **septic shock** are aimed at rapidly establishing the diagnosis and restoring mean arterial pressure to 65 to 75 mm Hg to improve organ perfusion. The response to resuscitation should be monitored closely by frequent reassessment of tissue perfusion.

Clinical clues to tissue perfusion include skin temperature, mental status, and urine output. Lactic acid measurements